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Application of Modeling Drugs in Animal Models of Chemical Phlebitis: Review

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Abstract

Objective: This review aims to determine the impact of different drugs and methods on the successful establishment of an animal model for chemical phlebitis (CP). **Design:** Search the Cochrane Library, ProQuest Academic Journal Library, PubMed, Web of Science, Ovid, Embase, CINAHL complete (EESCO) and other related databases to determine the literature. Screen out articles consistent with this review and summarize them. **Results:** Since the establishment of the database, a total of 1463 articles have been retrieved. After reading the title, abstract and full text, and excluding non-related and duplicate articles, 22 reports were finally included. Among them, there are 8 articles using different medication methods to compare the effects of establishing a CP model. The included articles explored the effects of different animal models, drug types, and their dose, concentration, speed, and time on the CP model. **Conclusion:** The factors of dose, concentration and time were positively correlated with the incidence of CP. The effect of speed factors on CP and the results of different animal models are inconsistent. It requires further research in the future.

Keywords

Chemical Phlebitis, Animal Model, Drug

1. Introduction

Chemical phlebitis (CP) is a sterile inflammatory reaction caused by the infusion of low pH, high osmotic pressure, high concentration of drugs, and produces chemical stimulation of the intima, vascular endothelial damage and phlebitis as well [1] [2] [3]. Clinical manifestations are local venous redness, fever, pain, swelling, and/or palpable induration [2]. The incidence of CP exceeds is 57.6% [2] [4]. The high incidence of CP inevitably leads to the removal of the catheter

and shortens the indwelling time [2] [4].

Researches on the CP have become a hot topic at home and abroad, and have been getting more results. In particular, more achievements have been made in animal experimental research. Application of clinically used stimulant drugs to the veins of animals can establish a CP animal model, and prevent and treat drugs before or after modeling [1] [5] [6]. The method of infusion is reproduced below (**Figure 1**). The data and results of these experimental studies have greatly contributed to the clinical prevention and treatment of CP.

Currently, the veins of rabbit ear and mouse tail are usually used for puncture modeling. However, the veins of these animal models are susceptible to factors, such as the dose, concentration, speed, and timing of the drug, causing local adverse reaction. As a result, this paper reviews recent advances in modeling drugs for animal models of CP.

2. Method

In order to accurately apply the modeled drugs, the animal model of CP was effectively established. The current status of application of CP animal model drugs was searched. The databases searched were Cochrane Library, ProQuest Academic Journal Library, PubMed, Web of Science, Ovid, Embase, CINAHL complete (EESCO), being the limits articles published since the establishment of the databas, and studies in English, Chinese. "chemical" OR "chemotherapy" OR "chemotherapeutic" OR "infusion" AND "phlebitis" phlebitis, "intravenous" OR "vein" OR "blood vessel" AND "damage" AND "animal" OR "rabbit" OR "mouse" OR "dog", "model" OR "drug" and other keywords are searched. A total of 1463 related articles were retrieved. By reading the titles and abstracts of the literature, articles such as non-animal experimental research and application of drug modeling were excluded. 55 articles were initially screened, 33 articles were excluded by reading the full text, and 22 articles were rescreened (**Figure 2**).

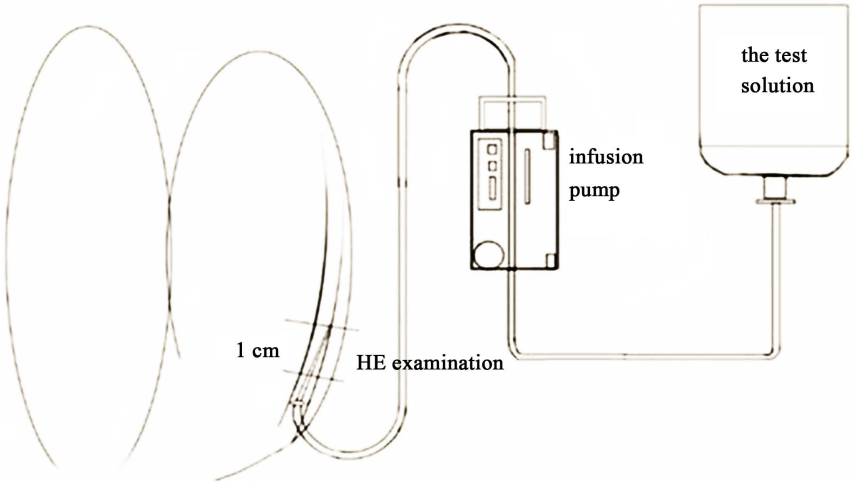

Figure 1. Infusion method for rabbit model of CP (Jing Zhang *et al*., 2016).

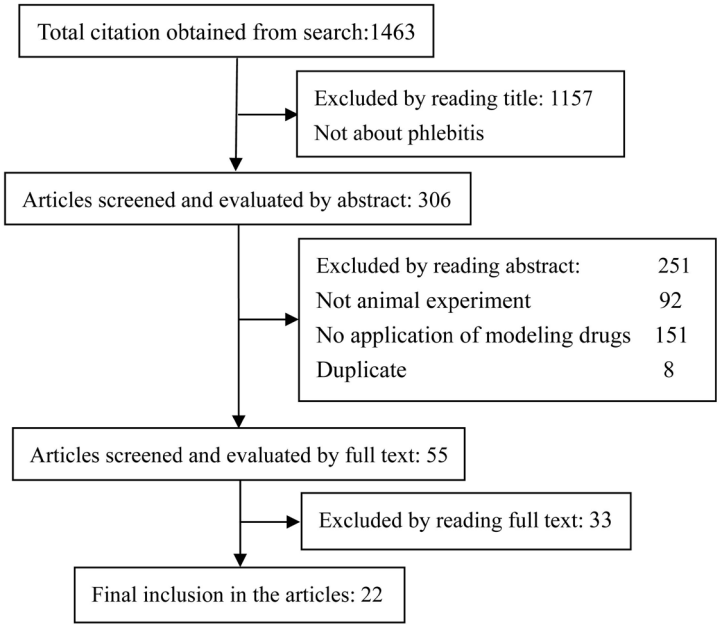

Figure 2. The process and results of screening articles.

3. Results

3.1. Establishment of an Animal Model for CP

3.1.1. Establishment of Rabbit Model

First, 1 - 2 d before the experiment, the researchers use depilatory agents (8% sodium sulphides) or razors to remove rabbit hair [4] [6] [7]. A 24G venous indwelling needle is utilized to select the ear vein at a distance of 1 - 3 cm from the tip of the ear as the puncture site, marking them with gentian violet/methyl violet solution; meanwhile, using 2% - 3% sodium pentobarbital, 10% chloral hydrate or ketamine before puncture. Perform anesthesia with abdominal, intravenous or intramuscular injection [8] [9]. After anesthesia, obtain the dose according to rabbit body weight, body surface area, or on the number of "one" (**Table 1**). After modeling, rabbit ear veins were examined by naked eye or light transmission for leakage. It can be considered as a successful modeling if no leakage [10] [11] [12] [13].

3.1.2. Establishment of Mouse Model

According to the diameter of the blood vessel, different types of needles are selected (for example, the mouse uses the 7# scalp needle) to puncture the mouse tail vein [14] [15]. Intraperitoneal injection of mice with diazepam and ketamine prior to puncture [15]. After anesthesia, puncturing the proximal and middle 1/3 of the mouse tail vein, and calculating drug dose by weight and infusion. After modeling, the diameter of the mouse tail was observed by an electronic digital caliper to observe the degree of swelling. The degree of swelling is calculated as swelling (%) = (the diameter of the mouse tail after treatment − the diameter of the mouse tail before treatment)/the diameter of the mouse tail before treatment × 100% [5] [14] [15].

Table 1. Comparison of dose methods for establishing a rabbit model.

Calculation	Unit	Method	Formula	Advantage	Disadvantage	Mainly References
Body weight	mg/Kg or mL/Kg	It is known that the dose of A animal per kg body weight is found by looking up the table (W)	Dose of B animals (mg/Kg) = dose of W × A animals (mg/Kg)	Lookup table calculation is convenient and accurate; the most commonly used calculation method	The conversion process is more complicated	[1] [5] [6] [9] [11] [14] [15] [16] [17] [18]
Body surface area	mg/m^2	According to Meeh-Rubner's formula, K is a constant 10.1, W is the body mass, in g	$A = K \times (W^{2/3})/10000$	Simple calculation	The K value reports are slightly different, and the estimated value is rough.	[10] [13]
Number	one of a pair	-	-	Simple	Inaccurate	[17] [19]

3.2. Modeling Drugs for Animal Models of CP

In experimental studies, drugs that are highly irritating, high in the concentration, high in the osmotic pressure, and low in the pH , which will be used to establish vascular models (Table 2).

3.2.1. Vinblastine

Commonly used vinorelbine (VNR) and vincristine (VCR), which are lipophilic drugs that directly cause damage to vascular endothelial cells. They are highly osmotic and can penetrate into extra vascular tissues, causing local vascular inflammatory reactions and imbalance of osmotic pressure inside and outside the cell membrane. Changes in pH, cause severe phlebitis and thrombosis [1] [12]. Wang *et al*. [13] according to the dose of human chemotherapy, intravenous low-dose (12.5 mg/m^2), medium dose (25 mg/m^2) and high dose (50 mg/m^2) VNR in rabbit ears, while the control group is injected with 10 mL of normal saline. The infusion pump is utilized to control the rate, and the infusion is completed in 15 min. The results show that the medium dos and high dose of VNR have typical phlebitis pathology at 48 h.

3.2.2. Doxorubicin

Doxorubicin (DXR) is a foaming agent chemotherapeutic drug, which easily damages cell membrane lipids and DNA, causing chemical damage to blood vessels, and manifesting as local redness, pain, and even local chondrocyte necrosis [21] [22]. Wang *et al*. [22] found that low-speed (60 mL/h), high concentration (0.20%), high capacity (20 mL) of the ear vein intravenous administration are relative to high speed (90 mL/h), low concentration (0.05%), low volume (10 mL) administration. Besides, the degree of phlebitis was observed by the naked eye, and the inflammatory infiltration of vascular endothelial cells was more serious under the microscope.

3.2.3. 20% Mannitol

As a hypertonic dehydration solution, 20% mannitol increases plasma and tissue osmotic pressure during infusion, resulting in dehydration of vascular

Table 2. List of commonly used drugs for animal models of CP from 2008 to 2018.

Reference, Year	Animal	Drug	Dose (mg/Kg)	Concentration (mg/mL)	Speed (mL/min)	Infusion time (min)	Frequency (Times/d)	Continuous dosing days (d)	Instrument for controlling speed
Fu (2018) [9]	Japanese white rabbit	VNR	0.5	-	0.5	-	1	2	-
Dan (2015) [12]	Rabbit	VNR	-	-	1.8	5	-	-	-
Wang (2014) [13][a]	Rabbit	VNR	12.5/25/50[b]	1	-	15	1	1	Infusion pump
Kohno (2008) [20][a]	Japanese white rabbit	VNR	1.5	0.6/0.3	-	-	1	2	Peristaltic pump
Ge (2017) [1]	Japanese white rabbit	VNR	3	-	5k	30	1	2	-
Wang (2014) [14]	New Zealand rabbit	VNR	5	-	2l	-	-	-	-
Kohno (2009) [21]	Japanese white rabbit	VNR	-	0.6	5k	30	-	2	-
Wang (2014) [14]	C57 Mouse	VNR	37.5	10h	0.75[m]	-	-	-	-
Zou (2017) [5]	Mouse	VNR	56.25	10	0.25[m]	-	1	1	-
Shen (2017) [15][a]	C57 Mouse	VNR	18.8/28.1/ 37.5/56.3/75	2.5/5/10	0.15/0.3/0.75[m]	10	-	7	Bolus pump
Zhang (2016) [6][a]	New Zealand rabbit	VCR	0.2	-	0.5	6/12/18/24[p]	-	-	Infusion pump
Kohno (2009) [21]	Japanese white rabbit	DXR	-	1.4	2k	120	-	3	-
Shen (2017) [9]	New Zealand rabbit	DXR	20[b]	2	1.5	-	1	3	-
Wang (2015) [22][a]	Japanese white rabbit	DXR	-	0.05/0.1/0.2[g]	0.5/1/1.5	-	-	-	-
Li (2018) [16]	Japanese white rabbit	Mannitol	4d	-	1	-	2	7	-
Zhang (2012) [23]	Japanese white rabbit	Mannitol	2.5[d]	-	0.5	-	2	2	-
Ge (2014) [24]	New Zealand rabbit	Mannitol	2.5[d]	-	-	5	1	3	Microinjection pump
Song (2014) [11]	New Zealand rabbit	Mannitol	2.5[d]	-	8	-	2	5	-
Tang (2017) [25][a]	rabbit	Mannitol	2.5[d]	-	-	-	1	0.5/1/2/3/4	-
Zhang (2016) [26]	New Zealand rabbit	Mannitol	2.5[d]	-	-	-	1	5	-

Continued

Chen (2014) [17]	New Zealand rabbit	Mannitol	10[c]	-	-	15	1	5	-
Zhang (2013) [4]	New Zealand rabbit	Mannitol	2.5[d]	-	0.5	-	2	2	Microinfusion pump
Mo (2015) [19]	New Zealand rabbit	Mannitol	10[c]	-	-	15	-	-	-
Kuwahara (2009) [27][a]	Japanese white rabbit	AF	-	-	5[k n]/15[k o]	-	1	1[q]/3[r]	Infusion pump
Yang (2017) [18][a]	Rabbit	Amiodarone	8[e]/20[f]	1.5[i]/1.8[j]	-	1/2/3/4/5[p]	-	-	-

"a" in the reference represents the treatment of different methods; In the dose, "b" unit is mg/m^2, "c" unit is mL/single, "d" unit is mL/Kg, "e" is 8 min before infusion, "f" is 6 h after infusion; In the speed, "k" unit is mL/Kg/h, "l" unit is mg/min, "m" unit is μL/s, "n" means continuous infusion, "o" means intermittent infusion; In the infusion time, "p" unit is hour; In the continuous dosing days, "q" means continuous infusion, "r" means intermittent infusion; "VNR" means Rvinorelbine, "VCR" means Vincristine, "DXR" means Doxorubicin, "Mannitol" means 20% Mannitol, "AF" means 3% amino acid/7.5% glucose solution; "-" in the full table means no.

endothelial cells and local platelet aggregation, thereby inducing vascular endothelial injury and apoptosis. At the same time, the release of prostaglandins activates inflammation, Mediation and leukocyte invasion, and release of histamine causes vasoconstriction and hardening [11] [16] [17] [19]. Experimental studies often use 2.5 mL/Kg doses or 10 mL infuse into the ear vein, and the model of CP was established by continuous drug for 2 - 7 days (**Table 1**). Tang *et al*. [25] showed that the main component of fibrin sheath contains red blood cells, thrombus, collagen fibers, cellulose and some cellular components, which is found by HE and Masson staining, by using the method of the infusion of 20% mannitol in rabbit ears.

3.2.4. Parenteral Nutrition Solution

Parenteral nutrition solution (PPN) is a hypertonic (600 - 900 mOsm/kg), acidic solution, causes chemical stimulation of peripheral veins, venous injury and CP [27]. Kuwahara *et al*. [27] used 3% amino acid/7.5% glucose solution (AF), osmotic pressure 856 mOsm/kg, pH 6.6, modeling rabbit ear vein. The results showed that there was a significant venous endothelial cell loss and peril vascular tissue edema in the continuous infusion group (5 mL/kg/h, 24 h), while the intermittent infusion group (15 mL/kg/h, 8 h × 3 d) had no significant changes in the veins.

3.2.5. Amiodarone

The pH value changes from 2.5 to 4.0, which is highly irritated to blood vessels and easily damages blood vessels, causing CP [18]. Yang *et al*. [18] showed that a moderate inflammatory reaction is observed under the microscope, when the rabbit ear vein infusion lasts for 3 h, through using the amiodarone model. Besides, as the infusion time prolongs, the inflammatory infiltration range will expand, and a large number of necrotic cells and severe vascular endothelium could be observed in the lumen after 5 h.

3.3. The Key Factors Affecting the Successful Establishment of CP

Dosing amount, concentration, speed and time are the key factors affecting the successful modeling of CP. Through the reading of the literature, there are 8 articles using different methods to compare the effects of establishing a CP model. The methods have their own advantages and disadvantages in the application of modeling (Table 3).

3.3.1. Medication Dose

When a large amount of drug flows into the vein, which continues to stimulate the inner wall of the blood vessel, causing harm to the wall. As the dose increases, the time for the drug remaining in the blood vessel is prolonged, and the risk of CP increases as well [15] [22]. Wang *et al*. [13] indicated that the incidence of phlebitis in each group was 42.9%, 85.7% and 100% respectively after injecting low, medium and high doses of VNR into rabbit model.

3.3.2. Medication Concentration

The high concentration on the drug entering the vascular drug, the large amount of the drug in contact with the vascular endothelium, and the high degree of damage to the blood vessel and surrounding tissues, which will be more likely to cause the tissue damage [15] [20] [22]. Kohno *et al*. [20] found that venous endothelial cell shedding, inflammatory cell infiltration, high edema in the group of high-concentration and low-speed (concentration 0.6 mg/mL, speed 5 mL/Kg/h) infused with VNR in the rabbit ear vein, slightly higher than the low-concentration high-speed group (a concentration 0.3 mg/mL, speed of 10 mL/Kg/h). However, the effect of the two groups was not statistically significant ($P > 0.05$). The difference of epidermal degeneration between these two groups had statistically significant ($P < 0.05$) due to the drug input of vein, but some of drug contacts to the inner wall of the blood vessel, thereby stimulating the damage to the vascular endothelium and increasing the permeability of the blood

Table 3. Advantages and disadvantages of different methods in the application of CP modeling drugs.

Method	Advantage	Disadvantage	Mainly References
Dose	There are conversion formulas such as weight or body surface area; More accurate calculation	The effective amount used in different animals is inconsistent; Excessive dose can cause death of small animals	[13] [15]
Speed	Fast onset, high bioavailability, easy to control blood concentration	The speed is difficult to control, resulting in inaccurate results; Need infusion pump, syringe pump and other instruments to control the speed	[15] [21] [22] [27]
Concentration	Simple and convenient to use the dilution method	There is no standard conversion formula to rely on; Inaccurate estimates can lead to animal poisoning reactions	[15] [21] [22]
Time	Effectiveness, increase the success rate of modeling; Correlation, associated with dose, speed, and concentration	There is a lack of standard standards for medication time, time interval and days of modeling	[18] [25] [27]

vessel. Meanwhile, drug in the lumen penetrates into the surrounding tissue of the blood vessel, and reaches the epidermis, causing epidermal degeneration. In addition, the drug concentration of the mouse model was divided into high-concentration group (10 mg/mL), medium-concentration group (5 mg/mL) and low-concentration group (2.5 mg/mL) under the same dose and speed.

3.3.3. Medication Speed

When the drug enters the blood in a low speed, it gradually forms a laminar flow with the blood and mixes with each other. If the blood cannot fully neutralize the drug, the drug contacts stimulate the vascular endothelial cells, causing damage [20] [22]. Kohno *et al*. [20] concluded that at the same concentration, low speed group (5 mL/Kg/h) is more easily to cause vascular endothelial cell shedding, inflammatory cell infiltration, epidermal degeneration than high speed group (15 mL/Kg/h). However, some scholars believe that when the drug speed is greater than the blood flow rate, the blood cannot dilute the drug concentration in time, thereby aggravating the chemical stimulation of the blood vessel to the vascular endothelium, increasing the permeability of the blood vessel, and causing the drug to ooze out to the surrounding tissue of the blood vessel. Besides, the damage to surrounding tissues [15] [22].

3.3.4. Medication Time

When the stimulant drug is put into the vein, which will stimulate the blood vessel to damage the vascular endothelium; and if the infusion continues, the drug accumulates in the damaged area, surpassing the stress ability of the blood vessel. As a result, it will damage the intima of the blood vessel, and aggravate the occurrence of phlebitis as well [20] [22] [27]. Zhang *et al*. [3] studied the severity of phlebitis by searching the length of VCR infusion time. This study found that phlebitis was respected by the naked eye after 12 h, and the loss of venous endothelial cells was observed by histopathology after 6 h. As a result, longer infusion time, the more severe phlebitis. Tang *et al*. [25] took samples of HE and Masson at different time (12 h, 1, 2, 3, 4 d) after 20% mannitol modeling, and found that fibrin begin to form in the vascular cavity after 12 h administration. With the prolonged administration time, the percentage of cross-sectional area accounting for the lumen area (%) also increased significantly ($P < 0.001$).

4. Discussion

A number of studies have established animal models of CP and then given different interventions to prevent and treat phlebitis. The success of CP directly affects the subsequent experimental results.

There are also many models for CP research. Currently, the types of animals are mainly rabbits and mice. Other animals have rarely been reported. Common rabbit species include Japanese white rabbits, New Zealand rabbits, and rabbits, weighing about 2.0 - 3.0 Kg (**Table 2**). Some researchers select male rabbits [20] [27], while the other part is not limited to males and females [18] [22] [25]. Be-

cause female rabbits not only have light weight, blood vessels are fine, but also secreted estrogen affects blood vessels. It is recommended that rabbits in the CP model be easy to select males in the future. The mouse model is also a small animal that is often selected. The use of standard inbred C57 mice increased the reliability of the experimental data relative to normal mice [14] [15]. However, the tail vein of the mouse is difficult to puncture. If the dose and concentration are too high, the mortality of the mice is increased. Shen *et al*. [15] injected VNR at the same concentration and speed into the tail vein of mice, and the dose varied from low to high of 18.8, 28.1, 37.5, 56.3 and 75 mg/Kg, respectively. The results showed that the higher dose of the drug, the higher incidence of sinusitis ($P = 0.006$), and the mortality of the high-dose group (56.3 and 75 mg/Kg) was 25.0%. 50.0%. In addition, they also found that the incidence of phlebitis in the three groups was 100%, no mice died in the high-concentration group, and the mortality rates in the middle and low-concentration groups were 50.0% and 62.5% respectively. The reason for explain that the size of mouse is smaller than the rabbit model, so the circulating blood volume is small. The one-time infusion amount cannot be effectively metabolized in the body, because too much accumulation is likely to result in poisoning death. Therefore, it is important for us to focus on maintaining the gradient and total amount of the while modeling the mice, which can help prevent the high mortality rate of the mice from affecting analysis results.

The drugs commonly used in modeling drugs are chemotherapeutic drugs such as VNR, DXR, etc., hypertonic drugs such as mannitol. The common feature of these drugs is that they are more irritating and easily damage blood vessels, making it easier to establish a CP model. Shen *et al*. [15] found that when the mice were injected with VNR at a dose of 37.5 mg/Kg and a concentration of 10 mg/mL, the incidence of phlebitis was 100% and no mice died; when the speed was 0.3 μl/s, the incidence of phlebitis was higher than in other speed groups (75% vs 33.3%, 25%), and no mice died. Therefore, it can conclude that the appropriate dose of VNR in mice is 37.5 mg/Kg, or 25 mg/m^2, the concentration is 10 mg/mL, and the speed is 0.3 μl/s [13] [15]. In addition, Shen *et al*. [10] simulated clinical chemotherapy courses, used a dose of 20 mg/m^2, a rate of 90 mL/h intravenous infusion of DXR which administered at the first, third, and fifth weeks to establish a model. This modeling mode is in line with the actual clinical use of drugs, and can provide a more accurate reference for the prevention of patients with CP. Mannitol is a commonly used dehydrating agent for brain damage. Because of high permeability, it is often used as a model drug for CP. However, some researchers injected 10 mL intravenously into the ear of each rabbit [17] [19] (**Table 2**). The weight of each rabbit is different, but the medication is the same, which will lead to inconsistent modeling effects and affect the experimental results. Therefore, the dose of the animal is recommended to use the body weight or surface area to convert the calculation, rather than counting the number of medications.

There are references using a single factor to compare the effects of different levels of parameters on the establishment of CP [13] [18] [25] (**Table 3**). A number of factors were combined to compare the effects of the model establishment, such as the combination of dose, concentration and speed, the combination of speed and number of days of administration [15] [22] (**Table 3**). There are even simulated clinical rinsing and before and after infusion to observe the impact on the CP model [20].

At present, the researchers agree that factors such as dose, concentration and time of administration are positively correlated with vascular endothelial injury. Therefore, the higher the dose, the higher the incidence of CP. But, researchers at home and abroad hold opposing views on the effects of drug rates on CP. One view is that low-speed medication is easy to cause CP, the other is that high-speed medication is easy to cause CP. Kuwahara *et al*. [27] injected AF into the rabbit ear vein at low-speed (5 mL/Kg/h) and high-speed (15 mL/Kg/h), and found that the low speed group is more prone to phlebitis than the high speed group ($P < 0.05$). Shen *et al*. [19] found that the incidence of CP in the high speed group (0.75 μl/s), medium-speed group (0.3 μl/s) and low speed group (0.15 μl/s) of VNR in the tail vein of mice is 33.3%, 75.0% and 25% respectively. The incidence of phlebitis in the moderate speed group was higher than the low speed group ($P < 0.05$). What's more, there is no mouse died in the middle and low speed groups, while 5 mice died in the high speed group. The reason explained for the results may be the differences in animal models, the different anatomical locations of the mouse tail and the rabbit ear vein, the thickness of the wall and the ability to tolerate stimulating drugs, which may require further research in the future.

5. Conclusion

Not only will accurate use of animal models pave the way for further prevention and treatment of CP, but also provide a reference for the clinical rational use of drugs. It can be viewed on this review that rabbits are mainly modeled animals, followed by rodents, and other large animals are rarely reported in the experimental studies. The size of rabbits and mice is very small compared to humans, so their circulatory and vascular conditions are quite different from those of clinical patients. In the future, studied animals should be closer to human body types, and also can add animal models simulating clinical patients, such as various types of cancer, diabetes, and cerebral edema. In the current research, the drug dose is calculated by the body weight or body surface area of the animal, and only a few researchers use the amount of modeling drugs as the units according to the number of animals. Although this method is simple, it will have a negative effect on the research result. Therefore, it is not recommended to use drugs based on the number of animals. Besides, in terms of the speed effects on CP, altered animal models present different results and conclusions, which need further research and discussion. Recently, despite the fact that there are many

types of drugs for modeling phlebitis, the drugs used in the specific experiments are relatively simple, and they are not fully compatible with the actual clinical combination. In the future research, modeling drugs can be diversified and more in line with clinical practice.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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